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54: Title of invention - Method of manufacturing copolymer

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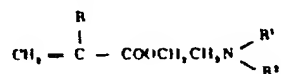74: Representative - Patent Attoerney Shigeru Tsukimura and one other

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Specification

1. Title of invention
   A method of manufacturing copolymers

2. Claims:
(1) A method of manufacturing copolymers in which (A) basic monomer
having the general formula,

$$CH_2 = \overset{\overset{\displaystyle R}{\displaystyle |}}{C} - COOCH_2CH_2N\begin{matrix} \diagup R^1 \\ \diagdown R^2 \end{matrix}$$

(In the formula, R is hydrogen or methyl group; R1 and R2 are C1 - C3
alkyl group.), (B) water insoluble monomer or monomer which is hardly
soluble in water, and (C) water soluble monomer are copolymerized,
whereas the concentration of (A) is 10 - 65 weight % and (B) is 8 - 45
weight %, and the weight ratio of (B)/(C) is 2/1 - 1/7.

3. Detailed explanation of the invention.
The present invention refers to a method of manufacturing copolymers,
where the solubility of the copolymer is influenced by the pH value. In
other words, the present invention relates to a method of manufacturing
the copolymer, whereas the copolymer is soluble in water at pH 8.5 or
lower; however, the copolymer is substantially insoluble in water at
pH 9.5 or higher.
There are several copolymers showing variable solubility according to
the pH of the medium. For example, although polyvinylacetaldiethylamino
acetate is insoluble in water at neutral pH range, this compound is   •
soluble in water at pH 5.8 or lower. On the other hand, although co-
polymer of vinylpyrridin and acrylic acid is soluble in water when the
pH is lower than 4 or when the pH is higher than 7.4, this compound is
insoluble in the pH range between 4 and 7.4. However, copolymers show-
ing the solubility in neutral and acidic water, but showing the insolu-

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bility in alkaline water and at the same time, showing variable solubility in a narrow range of pH are not known.

The present invention provides a method of manufacturing pH sensitive copolymer which is insoluble in alkaline water (pH 9.5 or higher), but is soluble in slightly alkaline and acidic water (pH is less than 8.5). When a surfactant capable of increasing the solubility of the copolymer exists, the copolymer obtained by the method described in the present invention can show a large ratio of solubilizing time of the said soluble pH range and insoluble pH range (Hereinafter, this is called solubility ratio.).

In other words, the method of manufacturing copolymer described in the present invention consists of copolymerization of (A) basic monomer having the general formula,

$$CH_2 = C - COOCH_2CH_2N \underset{R_2}{\overset{R_1}{\diagdown}}$$

(In the formula, R is hydrogen or methyl group; R1 and R2 are C1 - C3 alkyl group.), (B) water insoluble monomer or monomer which is hardly water soluble, and (C) water soluble monomer, whereas the concentration of (A) is 10 - 65 weight %, preferably 15 - 55 weight %; the concentration of (B) is 8 - 45 weight %, preferably 10 - 40 weight %, and the weight ratio of (B)/(C) is 2/1 - 1/7, preferably 3/2 - 1/6.

The basic monomer (A) having the said general formula is the major monomer ingredient in order to obtain the pH sensitive copolymer described in the present invention and can be one or more than two kinds of the following compounds; these are acrylic acid N,N-dimethylaminoethyl, methacrylic acid N,N-dimethylaminoethyl, acrylic acid N,N-diethylaminoethyl and methacrylic acid N,N-diethylamino ethyl.

Monomer (B) which is water insoluble or is hardly soluble in water contributes significantly the expansion of insoluble pH range of the pH senstive copolymer, and one or more than two kinds of the compounds selected from the group of compounds; these compounds are acrylic acid ester, methacrylic acid ester, crotonic acid ester, itaconic acid ester, vinyl acetate and styrene. However, in case of employing corresponding alkyl ester of acrylic acid, methacrylic acid, crotonic acid, itaconic acid as the monomer (B), the chain length of the said alkyl group may be 1 - 8 because the speed of solubilization of the compound in weak alkaline water containing copolymer generated can be delayed when the carbon chain length of alkyl group binding to ester is too long. The preferable compounds are methyl acrylate, ethylacrylate, butylacrylate, methyl-methacrylate and ethylmethacrylate.

The water soluble monomer (C) contributes the expansion of soluble pH range of the pH sensitive copolymer, and is selected from the group of compounds consisting of N,N-dimethylaminopropyl acrylic acid (methacrylic acid) amide, N,N-dimethylacrylic acid (or methacrylic acid) amide, 3-hydroxypropylacrylic acid (or methacrylic acid), polyethyleneglycol

(in all cases, $\bar{p}$ = 2 - 30) and ester of acrylic acid or methacrylic acid; and one or more than two kinds of the said compounds can be used in the present invention.

The purpose of the present invention is to manufacture copolymer which is insoluble in alkaline water of approximately pH 9.5 or higher, but is soluble in weak alkaline or acidic water of approximately pH 8.5 or lower, and at the same time, which shows a large solubility ratio under the presence of surfactant. In case of copolymerizing the said three kinds of monomer ingredients, the concentrations of the said monomers must be regulated properly as described below; in other words, the concentration of the monomer (A) in the monomer mixture is 10 - 65 wt%, preferably 15 - 55 wt%; and the concentration of the monomer (B) is 8 - 45 wt%, preferably 10 - 45 wt%, and at the same time, the weight ratio of the monomer (B) to the monomer (C) is 2/1 - 1/7, preferably 3/2 - 1/6. When the relative concentration of the said three monomers is out of the said range, the copolymer showing distinct pH sensitive nature described above and large solubility ratio under the presence of surfactant can not be obtained.

The copolymerization of three monomer ingredients can be carried out by radical polymerization under normal or positive pressure, preferably. The solvents employed in the said polymerization may be acetone, benzene, toluene, chloroform, ethylacetate, isopropanol, dimethylformamide, dimethyl-sulfoxide, etc. or a mixture solvenet system consisting of the said solvents or solvent system containing water. The radical polymerization initiator may be azo-bis-isobutylonitrile and triphenylmethylazobenzene. The concentration of the said polymerization initiator in the system containing the said three ingredients may be 2 - 100 millimol.

The polymerization temperature and the polymerization time are determined according to type of polymerization solvent system and the composition of three monomer ingredients in the reaction mixture. In generally, the reaction temperature may be 40 - 90° C and the reaction time may be 5 - 20 hours. The concentrations of three monomer ingredients can be determined properly according to the type of polymerization solvent system, polymerization temperature, and the polymerization initiator. However, it is usually 20 - 80 wt%.

As described clearly above, the copolymer described in the present invention is insoluble in alkaline water of pH 9.5 or higher, and is soluble in weak alkaline and acidic water of pH 8.5 or lower. Consequently, the copolymer is able to protect the content from the outer environment, and to release the content when the outer condition is weak alkaline or acid. Thus, the said copolymer can be used as an excellent coating agent. For example, it is known that the pH of content in the stomach of a patient suffering with hypacidity or anacidity is occasionally neutral. The present invention can be used as the coating agent for the medicine given to the said patient. In other words, when the stomach soluble medine is coated with the said copolymer, the film dissolve in the stomach, and the effective medicine can be delivered directly into the

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stomach.

On the other hand, when the copolymer described in the present invention can be used as the coating agent for a laundering adjuvant, especially rinsing agent adjuvant, the content can be released during the rinsing period of the washing cycle, and the effectiveness of the adjuvant is considerably promoted in this case.

Some practical examples of the present invention shall be demonstrated in the following.

Practical example 1:

Twenty-one g of methacrylic acid N,N-dimethylamino ethyl, 18.0 g of methyl methacrylate, 21.0 g of N,N-dimethylaminopropyl methacrylic acid amide and 50 g of benzene were placed in a 200 ml 4 neck flask consisting of a stirrer, thermometer, reflux condencer and nitrogen gas introducing tubing. Nitrogen gas was introduced into the flask for 15 min with a constant stirring, and then the flask was heated in a hot bath (70° C). When the temperature of the content in the flask reached at 65° C, 0.72 g of azo-bis-isobutylonitrile dissolved in 10 g of benzene was added as the polymerization initiator. The polymerization was carried out at 70° C for 7 hours with a constant stirring.

Two liters of hexane was placed in a 3 L beaker, and the benzene solution containing the copolymer was slowly poured into the hexane while stirring and the copolymer was precipitated. The copolymer was washed with 500 ml hexane twice, and was dried under reduced pressure. Dried copolymer was pulverized. The yield was 55.5 g.

The polymer obtained was dissolved in acetone (the concentration was 30 wt %.), and the polymer solution was poured over a teflon sheet. After drying in air, a film of 0.1 mm ± 0.01 mm in the thickness was prepared. The said film was allowed to stand in a constant temperature and humidity room (20° C, 60% RH) for 24 hours. The film was cut into 5 x 5 mm, and the solubility of the film was tested.

The solubility of the test film was determined by the following method. In other words, solutions showing various pH's were prepared by adding various amount of sulfuric acid or sodium hydroxide in tap water and 100 ml of the said solution was placed in a 200 ml beaker. One sheet of film (5 x 5 mm) was placed in the said solution showing various pH's. While mainitaining the liquid temperature at 25 ± 1° C, the solution containing the film was stirred with a magnetic stirrer, and the solubility of the film was observed. When the film did not dissolve after 2 hours, the film was defined as insoluble form. When the shape of the film was altered with time, the time required for complete dissolution was determined. The result is shown in Table 1.

Table 1:

pH of solution	Solubility
10.4	insoluble
9.6	insoluble
8.3	20 min

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6.5	10 min
5.1	7 min

Comparative example 1:
Twenty-eight g of methacrylic acid N,N-dimethylaminoethyl, 24.0 g of
methyl methacrylate and 42 g of benzene were placed in a 200 ml 4 neck
flask consisting of a stirrer, thermometer, reflux condenser and nitro-
gen gas introducing pipe. Nitrogen gas was introduced into the flask
for 15 min with stirring. The flask was then heated in a hot water
bath (70° C). When the temperature of the content in the flask
reached at 65° C, 0.69 g of azo-bis-isobutylonitrile dissolved in 10 g
of benzene was added to the flask (as the polymerization initiator).
The polymerization was carried out at 70° C for 7 hours with a constant
stirring. Thus, 47 g of copolymer was obtained in the same manner as
described in the practical example 1.

Comparative example 2:
Thirty g of methacrylic acid N,N-dimethylaminoethyl, 30.0 g of N,N-di-
methylaminopropylmethacrylic acid amide and 50 g of benzene were placed
in a 200 ml 4 neck flask consisting of a stirrer, thermometer, reflux
condenser and nitrogen gas introducing tubing. Nitrogen gas was intro-
duced into the flsk for 15 min with a constant stirring and the flask
was heated in a hot water bath (70° C). When the temperature of the
content of the flask reached at 65° C, 0.60 g of azo-bis-isobutylonitrile
dissolved in 10 g of benzene as the polymerization initiator was added
to the flask. The polymerization was carried out at 70° C for 7 hours
with a constant stirring. Then, 56 g of copolymer was prepared in the
same manner as described in the practical example 1.
The copolymer obtained was dissolved in acetone (the concentration was
30 wt%.). A film of 0.1 ± 0.01 mm in the thickness was prepared in
the same manner as described in the practical example 1, and the solubi-
lity was determined in the same manner. The copolymer obtained at the
comparative example 1 was also tested in the same manner as described
in the practical example 1. The result is shown in Table 2.

Table 2:

pH of solution	Solubility	
	Comparative example 1	Comparative example 2
10.4	insoluble	3 min
9.5	insoluble	3 min
8.3	insoluble	3 min
6.5	insoluble	2 min

Practical example 2:

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The weight ratio of methyl methacrylate (MMA) and N,N-dimethylaminopro-
pyl methacrylic acid amide (DMA) was set at 2/3, and the concentration
of methacrylic acid N,N-dimethylaminoethyl (DM) was changed. The copoly-
mer was then obtained in the same manner as described in the practical
example 1. The copolymer obtained was dissolved in acetone (the concen-
tration was 30 %.), and the solution was poured over the teflon sheet.
After drying in an air, a film of 0.1 $\pm$ 0.01 mm in the thickness was
obtained. After cutting the film into 5 x 5 mm, the solubility ratio
was determined. The solubility ratio was determined by the method
described in the following. In other words, 250 ppm of linear alkyl-
benzene sulfonate was dissolved in tap water, and the pH was adjusted to
10.3 with sodium hydroxide. Separately, 15 ppm of linear alkylbenzene
sulfonic acid was dissolved in tap water, and the pH was adjusted to 8.3
with sodium hydroxide solution. One hundred ml of the said solution was
placed in a 200 ml beaker, and one sheet of the copolymer sheet of 5 x
5 mm was placed in the beaker. The system was stirred with a magnetic
stirrer at 25 $\pm$ 1° C, and the time required for dissolving the film icom-
pletely was determined. The time required for dissolving the film in
the pH 10.3 solution was divided by the time required for dissolving the
film in the pH 8.3, and the solubility ratio was calculated. The result
is shown in Table 3.

Table 3:

a:	共重合組成中のDM の含有量(wt%)	b 溶解時間比		c 溶解性比
		pH 10.3	pH 8.3	
(1)	8	3.2	1.5	2.1
(2)	10	4.5	1.4	3.2
(3)	15	6.2	1.3	4.8
(4)	30	9.5	1.1	8.6
(5)	37.5	9.0	1.0	9.0
(6)	50	8.0	0.9	8.8
(7)	65	2.3	0.7	3.3
(8)	70	1.0	0.5	2.0

a: Concentration of DM
in the copolymer
composition (wt%)

b: ratio of dissolving
time

c: solubility ratio

Table 3 shows the time required for dissolving the film in the pH 10.3
solution and in the pH 8.3 solution, and contains the ratio of solubili-
zing time based on 10 min solubilizing time in the pH 6.5 solution
demonstrated in the practical example 1 (the ratio of dissolving time).
In order to obtain copolymer showing a large solubility ratio, the con-
centration of DM should be regulated in a specified range which was 10
- 65 wt %.

Practical example 3:
The weight ratio of methacrylic acid N,N-dimethylaminoethyl (DM) and N,

N-dimethylaminopropylmethacrylic acid amide (DMA) was set at 1, and the concentration of methyl methacrylate (MMA) was changed. Thus, copolymer was prepared in the same manner as described in the practical example 1. The solubility ratio was determined in the same manner as described in the practical example 2. The result is shown in Table 4.

Table 4:

a: 共重合体中のMMA 濃度(wt%)	b: 溶解時間比		c: 溶解性比
	pH 10.3	pH 8.3	
(1) 5	0.6	0.3	1.2
(2) 7.5	1.8	0.6	2.0
(3) 15	4.0	0.8	5.0
(4) 20	6.6	0.8	8.3
(5) 25 *	9.0	1.0	9.0
(6) 30 **	11.0	1.1	10.0
(7) 35	12.5	2.2	6.1
(8) 45	16.0	4.3	3.7
(9) 50	18.0	7.3	2.5

a: Concentration of MMA in the copolymer composition (wt%)

b: ratio of dissolving time

c: solubility ratio

* : Same as (5) in the practical example 2.
** : Same as the practical example 1.

As shown in Table 4, in order to obtain copolymer showing a large solubility ratio, the concentration of MMA should be regulated in a specific range which was 8 - 45 wt%.

Practical example 4:
Twenty wt% of methacrylic acid N,N-dimethylaminoethyl (DM) and 40 wt% of DM were used. The weight ratio of methyl methacrylate (MMA) and N,N-dimethylaminopropyl methacrylic acid amide (DMA) was changed. Thus, the copolymer was prepared in the same manner as described in the practical example 1. The solubility ratio of copolymer obtained was determined in the same manner as described in the practical example 2. The result is shown in Table 5.

Table 5:

d: 共重合体組成		e: 溶解時間比		f: 溶解性比
g: DM濃度(wt%)	h: MMA/DMA (重量比)	pH 10.3	pH 8.3	
(1)	1/8	0.7	0.4	1.8
(2)	1/7	1.5	0.4	3.8
(3) 20	1/6	2.2	0.5	4.4
(4)	1/3	2.8	0.5	5.6
(5)	1/1	11.8	1.5	7.9
(6) 40	3/2	15.0	3.3	4.5
(7)	2/1	17.5	5.3	3.3
(8)	3/1	21.0	9.5	2.2

d: Copolymer composition

e: ratio of dissolving time

f: solubility ratio

g: Concentration of DM

h: MMA/DMA ratio (weight ratio)

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According to the results shown in Table 5, it is noted that the solubility ratio was reduced when the weight ratio of MMA and DMA was not in the specified range even although DM or MMA was within the speficied range demonstrated in the practical example 2 or the practical example 3. (Table 5: (1) or (8).).

Consequently, in order to obtain copolymer showing an excellent solubility ratio, it is necessary to regulate the weight ratio of MMA and DMA to 2 : 1 - 1 : 7.

Application example 1:

Sixty weight parts of acetone solution of copolymer (15 wt%) obtained at the practical example 1 was sprayed onto 40 weight parts of distearyl dimethylammonium chloride (32 - 100 mesh) using a coating pan.

Five weight parts of powder obtained by the method described above and 95 weight parts of commercial detergent A (25 wt parts of sodium linear alkylbenzene sulfonate, 15 wt parts of zeolite, 45 wt parts of sodium sulfate and 15 wt parts of water) were mixed. Forty g of the said mixture was placed in a washer (volume of water : 30 liters), and clothes cotton towel and cotton underwears 2 kg) were washed for 10 min, and were rinsed twice with pooled water for 3 min. After drying in a room, the softeness of the cotton towel was evaluated. The commercial detergent A mixed with 4.1 wt % of distearyldimethylammonium chloride was employed as the control. The panel consisted of 10 examiners, and a pair comparison method was employed to evaluate the softeness. The result is shown in Table 6.

Table 6:

	Softening effect
Application example 1 is better.	8
Application example 1 is slightly better.	2
Same	0
Control is slightly better.	0
Control is better.	0

Practical example 5:

Twenty-one g of methacrylic acid N,N-dimethylaminoethyl, 6.0 g of methyl acrylate, 12.0 g of methyl methacrylate, 21.0 g of N,N-dimethylamino propyl methacrylic acid amide and 50 g of benzene were placed in a 200 ml 4 neck flask consisting of a stirrer, thermometer, reflux condenser and nitrogen gas introducing pipe. Nitrogen gas was introduced into the flask for 15 min with a constant stirring, and the flask was placed in a hot water bath (70° C). When the temperature of the content in the flask reached to 65° C, 0.73 g of azo-bis-isobutylonitrile dissolved in 10 g of benzene as the polymerization initiator was added. The polymerization was carried out at 70° C for 9 hours with a constant stirring.

The copolymer was precipitated by pouring the reaction mixture into hexane pool as described in the practical example 1. The copolymer was washed with hexane and was dried. Thus, 56 g of copolymer was obtained. The solubility ratio of the copolymer obtained was determined in the same manner as described in the practical example 2, and it was found that the ratio of solubility was 8.5.

Practical example 6:
A 17.5 g of methacrylic acid N,N-dimethylaminoethyl, 3.5 g of methacrylic acid N,N-diethylaminoethyl, 18 g of methyl methacrylate, 21.0 g of N-N-dimethylaminopropyl methacrylic acid amide and 30 g of acetone were placed in a 200 ml 4 neck flask consisting of a stirrer, thermometer, reflux condenser and nitrogen gas introducing tubing. The nitrogen gas was introduced into the flask for 15 min with a constant stirring, and the flask was placed in a hot water bath (60° C). When the temperature of the content in the flask reached to 55° C, 0.71 g of azo-bis-isobutylonitrile dissolved in 10 g of acetone as the polymerization initiator was added. The polymerization reaction was carried out for 10 hours at 60° C with a constant stirring. The copolymer obtained was diluted with acetone, and the concentration was adjusted to 30 wt%. The said diluted copolymer solution was poured onto teflon sheet, and a film was prepared. The solubility ratio of the film was tested in the same manner as described in the practical example 2, and it was found that it was 6.4.

Practical example 7:
A 21.0 g of acrylic acid N,N-dimethylaminoethyl, 18.0 g of methyl methacrylate, 21.0 g of N,N-dimethylaminopropyl methacrylic acid amide and 30 g of acetone were placed in a 200 ml 4 neck flask consisting of a stirrer, thermometer, reflux condenser and nitrogen gas introducing tubing. Nitrogen gas was introduced into the flask for 15 min with a constant stirring, and the flask was heated in a water bath (60° C). When the inner temperature reached 55° C, 0.74 g of azo-bis-isobutylonitrile dissolved in 10 g of acetone as the polymerization initiator was added. The polymerization was carried out at 60° C for 10 hours with a constant stirring.
The solubility ratio was determined in the same manner as described in the practical example 6, and it was 7.5.

Practical example 8:
A 21.0 g of methacrylic acid N,N-dimethylaminoethyl, 18.0 g of methyl methacrylate, 16.0 g of N,N-dimethylaminopropyl methacrylic acid amide, 5.0 g of methacrylic acid 2-hydroxyethyl, and 30 g of acetone were placed in a 200 ml 4 neck flask consisting of a stirrer, thermometer, reflux condenser, and nitrogen gas introducing tubing. Nitrogen gas was introduced into the flask for 15 min with a constant stirring, and the flask was heated at 60° C in a water bath. When the inner temperature reached 55° C, 0.73 g of azo-bis-isobutylonitrile dissolved in 10 g of acetone as the polymerization initiator was added. The polymerization was carried out at 60° C for 10 hours with a constant stirring. The solubility

ratio of the copolymer obtained was determined in the same manner as described in the practical example 6, and it was 8.0.

Practical example 9:
A 16.0 g of N,N-dimethylaminopropyl acrylic acid amide was used instead of N,N-dimethylaminopropyl methacrylic acid amide, and copolymer was prepared in the same manner as described in the practical example 8. The solubility ratio of the copolymer obtained was determined in the same manner as described in the practical example 6, and it was 7.8.

Practical example 10:
Monomers listed in Table 7 were used instead of methacrylic acid 2-hydroxyethyl, and copolymer was obtained in the same manner as described in the practical example 8. The solubility ratio of the copolymer obtained was determined in the same manner as described in the practical example 6. The results are shown in Table 7.

Table 7:

Type of monomer	Solubility ratio
N,N-dimethylacrylic acid amide	7.5
acrylic acid 2-hydroxyethyl	10.2
acrylic acid 2-hydroxypropyl	8.0
polyethyleneglycol methacrylate $(p = 5)$	9.5
methoxypolyethyleneglycol methacrylate $(p = 23)$	9.2